REMARKS

The Examiner has acknowledged Applicant's election with traverse of Group 1, claims 1, 4-13, 15-17, and 21. Applicants acknowledge that the restriction requirement is now final.

The Examiner has considered pending claims 1, 4-13, 15-17, and 21. The Examiner has withdrawn pending claim 35 as being drawn to non-elected inventions, and Applicants have canceled claim 35 without prejudice.

Support for new claim 36 may be found throughout the application as filed. See, for example, paragraphs 0091 and 0093, and Example 2.

The remainder of the Examiner's remarks are addressed below in the order they appear in the office action.

Claim rejections – 35 USC § 112

The Examiner has rejected claims 1, 4-13, 15-17, and 21 under 35 U.S.C. 112, first paragraph, as allegedly non-enabling for treating a neuronal deficiency caused by Parkinson's disease with any fraction of BM-derived cells to a recipient that has not undergone BM preconditioning, and by any route of delivery. The Examiner states that although the specification demonstrates that following transplantation of bone-marrow cells in mice, multiple neuronal cell surface markers are detected in the implanted cells, the specification "fails to teach the functioanl aspect of the cells, whether cells bearing a few neuronal cell markers would also have the function of neuronal cells, particularly in the case of treating Parkinson's disease, whether cells bearing a few neuronal cell markers would secrete dopamine, and to the extent it ameliorates a symptom of the disease" (page 5 of the office action). The Examiner further states that the post-filing data "is an addition to the original disclosure, and clearly the enablement of the instant claims is relied on the post-filing date data." Applicants respectfully traverse.

With respect to new claim 36, Applicants note with appreciation Examiner's statement that, "[A]pplicant appears to be the first to disclose a novel means of delivering bone marrow cells to the brain through intravenous route as opposed to direct brain tissue delivery...the

applicant may be entitled [to] a patent drawn to such a method of delivery [of] BM-derived cells to the brain." Accordingly, Applicants submit that new claim 36 is fully enabled and free of the prior art.

With respect to claims 1, 4-13, 15-17 and 21, Applicants request reconsideration of this rejection. The specification teaches that transplanted bone marrow cells will give rise to new neurons and predicts that these bone marrow-derived neuronal cells can compensate for the loss of functioning neuronal cells in diseases such as Parkinson's disease (see, for example, paragraphs 0030, 0038, and 0076 of the specification). The application specifically teaches methods of treating Parkinson's disease (PD) by administering bone marrow-derived cells. Performing these methods and achieving the outcome as claimed require no undue experimentation (as verified in the declaration dated 4/4/05). It appears the Examiner's rejection relates to the intended therapeutic use and an alleged lack of enablement for the claimed therapeutic use. Regarding the utility of claimed therapeutic uses, MPEP 2107.01 states

> ... therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States...Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

Accordingly, the claimed methods taught in the specification and based on the evidence and support provided in the examples are fully enabled as a person skilled in the art can practice the claimed methods without undue experimentation (as confirmed in the declaration). Likewise, the claimed therapeutic uses are enabled, as performing the claimed methods achieves the predicted therapeutic outcome (also as verified in the declaration; see remarks below regarding the validity of the post-filing data). Accordingly, the disclosure satisfies both the enablement and utility requirements.

The post-filing data substantiates the enabled methods of the claimed invention. This post-filing data demonstrates that bone marrow transplantation following MPTP-induced neurodegeneration in mice increased the number of dopaminergic neurons in the substantia nigra

and significantly increased dopamine transporter immunoreactivity in the striatum compared to non-transplanted, MPTP-treated mice. Further, bone marrow transplantation resulted in improved motor performance. The Examiner states "the specification as filed never contemplates the MPTP-treated mouse model, nor reasonably predicts the BM cells in the brain would provide neuronal function" (page 6 of the office action). However Applicants clearly teach that bone marrow-derived cells will give rise to neuronal cells in the brain; and neuronal cells inherently serve neuronal functions (see paragraph 76, for example: "Administration of bone marrow-derived cells to a subject results in the formation of new neurons, derived from the bone-marrow-derived cells, in the *nervous system* of the patient. Administration of bone marrow-derived cells results in an improvement, stabilization, or a reduction in the rate of progression of symptoms of a neuronal deficiency" *emphasis added*). Contemplation of the MPTP mouse model is not required to enable the methods of the claimed invention.

The Examiner also cites Fleming et al. to argue that the MPTP-toxin PD model is not predictive of human PD (page 7 of the office action). The statement of Fleming et al. relates to toxin models of PD focusing on the nigrostriatal pathway and the loss of dopamine, although no specific toxins are mentioned. Fleming et al. state that traditional toxin models "are limited in that they do not reproduce the full pathology and progression seen in PD, thus creating a need for better models. The recent discovery of specific genes causing familial forms of PD has contributed to the development of novel genetic mouse models of PD" (abstract). However Fleming et al. does <u>not</u> state that toxin models are unpredictive and in fact states that "these models have been important in our understanding of PD and *in the development of symptomatic treatments for the disease*" (*emphasis added*; abstract). Further, among the "better" and "novel" genetic mouse models of PD is α-Synuclein knockout mice, and α-Synuclein and MPTP act on the same molecular pathway (Dauer et al. 2002 PNAS (99):14524-14529, page 14524 first column, third paragraph and full article attached). Dauer et al. state that MPTP "causes a syndrome that mimics the core neurological symptoms and relatively selective dopamine (DA) neuron degeneration of PD" (page 14524, first column, second paragraph). Moreover, MPTP induces midbrain dopaminergic neuronal degeneration in the same nuclei in mice that degenerate in humans with PD (see German et al., abstract attached). Other artisans claim the MPTP model has certain advantages; for example, in a primate model MPTP resembles human PD with regard to the neuroanatomy of neurotransmitter loss (Eslamboli, abstract attached). The fact that "the biochemical and cellular changes that occur following administration of MPTP are remarkably

similar to that seen in idiopathic Parkinson's disease" (Smeyne and Jackson-Lewis, review attached) supports the argument that any functional improvement observed in the model can be predictive of improvement that would be observed in human PD.

The Examiner also contends that it is highly unpredictable whether the bone marrow-derived cells would engraft and home to the brain tissue and successfully mature into neuronal cells (pages 8-9 of the office action). In addition, the Examiner states that the specification fails to teach which fraction of bone marrow-derived cells is effective in neuronal progenitor cell homing and phenotype transformation. However as demonstrated in the MPTP mouse model, administration of unfractionated or whole bone marrow results in increased neuronal activity in the brain and improved behavior. As whole bone marrow achieves the desired outcome, and as whole bone marrow comprises all possible fractionations of bone marrow, cells and cells derived from both whole bone marrow as well as any fraction of bone marrow are within the scope of the claimed invention. Accordingly whole bone marrow may be fractionated to enrich for those bone marrow-derived cells that achieve the same or a similar outcome as whole bone marrow, as contemplated in the specification. Such fractionation and treatment of neuronal deficiency can be achieved using the same methods taught in the specification and declaration. Applicants note, however, that such fractionation is not a requirement of the claimed invention.

In response to the Examiner's rejection under 5 U.S.C. 112, first paragraph, for non-enablement, Applicants argue that the specification teaches the methods of the claimed invention and that these teachings are supported by the illustrative examples provided both in the specification and the declaration. The animal models substantiate the teachings of the disclosure as they provide working embodiments of the claimed invention and can be extrapolated to predict outcomes of the methods in humans. Decisions from the Federal Circuit clearly support the conclusion that if an in vitro model correlates with an in vivo activity, the in vitro model constitutes a working example. See MPEP 2164.02 citing *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention.... [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)" Further, in *In re Brana* the court states "If applicants

were required to wait until an animal naturally developed this specific tumor [lymphocytic tumors] before testing the effectiveness of a compound against the tumor in vivo...there would be no effective way to test compounds in vivo on a large scale."

It follows from the reasoning above that evidence obtained using an accepted in vitro animal model such as the mouse MPTP model constitutes a working example supporting in vivo efficacy. This evidence supports the enablement of the claimed methods for use of the claimed invention in humans. Applicants request reconsideration and withdrawal of this rejection.

Claim rejections – 35 USC § 102

The Examiner has rejected claims 1, 4-13, 15-17, and 21 under 35 U.S.C. 102(f), contending that the present Inventors did not invent the claimed subject matter. Inventors presume the Examiner has reached this conclusion based on the claims of co-pending U.S. application 10/688,747, for which the inventors are H. Blau, T. Brazelton, and J. Weimann. The 10/688,747 application claims priority to the present application, and the Examiner states that these two applications are of "common ownership". The additional inventor of the 10/688,747 application (Weimann) is included as this inventor contributed to the claimed subject matter of original claims 35-40 of the latter patent (these claims are not included in the present application). As the present application precedes the 10/688,747 application in filing date and as the present Inventors are also listed as inventors of the 10/688,747 patent, it is clear that Applicants Brazelton and Blau have invented the presently claimed subject matter; there is no evidence to suggest otherwise.

The Examiner further states that the commonly assigned application (10/688,747) would form the basis for a rejection under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f), or (g) and the conflicting inventions were not commonly owned at the time the invention in the present application was made. The present application precedes in filing date the 10/688,747 patent and the latter patent application claims priority to the present application. Therefore the 10/688,747 application cannot serve as prior art against the present application.

Double patenting

Claims 1, 4-13, 15-17, and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-21 of copending application 10/688,747. As this is a provisional rejection, Applicants respectfully traverse and request that this rejection be held in abeyance until the finding of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter in both applications.

CONCLUSION

In view of the above remarks, applicant believes the pending application is in condition for allowance.

Except for the fee for extension of time filed herewith, Applicant believes no fee is due with this response. However, if any additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. SUPP-P01-016 from which the undersigned is authorized to draw.

Dated: September 8, 2006

Respectfully submitted,

By _____

John D. Quisel
Registration No.: 47,874
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant